HIGH-AFFINITY ANTI-VEGF ANTIBODY

[0001] This application is a Continuation of co-pending application Ser. No. 16/067,931, filed on Jul. 3, 2018, which is the National Stage Application under 35 U.S.C. § 371 of International Application No. PCT/JP2017/000101, filed on Jan. 5, 2017, which claims the benefit under 35 U.S.C. § 119(a) to Japanese Patent Application No. 2016-001277, filed on Jan. 6, 2016, all of which are hereby expressly incorporated by reference into the present application.

TECHNICAL FIELD

[0002] The present invention relates to a high-affinity anti-VEGF antibody.

BACKGROUND ART

BACKGROUND OF THE INVENTION

[0003] Vascular endothelial growth factor (VEGF) can induce vasculogenesis (angiogenesis) in vivo, and is a heparin-binding growth factor that is specifically expressed in vascular endothelial cells. Human VEGF protein was purified and identified in 1989. The gene thereof has been cloned and thus the gene sequence has been determined.

[0004] VEGF can accelerate vasculogenesis, and all members belonging to the VEGF family bind to receptors (VEGFR) corresponding to respective family molecules existing on cell membrane surfaces and thus to activate cells. As a result of dimerization due to binding of VEGF, the group of these receptors undergoes auto-phosphorylation and is thus activated. VEGFR consists of seven immuno-globulin-like extracellular domains, one transmembrane domain, and one intracellular domain containing a tyrosine kinase region. VEGF-A can bind to VEGF receptor-1 (receptor Flt-1) and VEGF receptor-2 (KDR/Flk-1). Among VEGF receptors, particularly, VEGF receptor-2 mediates almost all known biological functions of VEGF. Regarding VEGF physiological activity and VEGF receptors, Marti et al., (Non Patent Literature 1: Angiogenesis in ischemic disease. Thromb. Haemost. 1999. Supplement 1: 44-52) and Matsumoto et al., (Non Patent Literature 2: VEGF Receptor Signal Transduction. Sci. STKE. 2001. re21) have studied in detail.

[0005] In the U.S. and Europe, Avastin® (bevacizumab) that is a recombinant anti-VEGF humanized monoclonal antibody is used for treatment of colorectal cancer, breast cancer, non-small-cell lung cancer, glioma in the central nervous system, and age-related macular degeneration (AMD). The sales of Avastin in 2013 reached US$ 6,746,000,000, but Avastin does not have high affinity for VEGF (Non Patent Literature 3: Aflibercept as a Treatment for Age-related Macular Degeneration. US Ophthalimic Rev. 2013. 6:58-63). Furthermore, the exclusive production and exclusive form of selling of Avastin force patients who need to use Avastin to pay high medical expenses. Therefore, development of a new anti-VEGF monoclonal antibody is required also from viewpoints of easing the burden of patients and reducing the costs of treatment.

[0006] Antibodies having affinity for VEGF higher than that of Avastin have been developed to date, and such antibodies exert tumor suppression superior to Avastin (Patent Literature 1: JP Laid-Open Publication No. 2013-502445).

CITATION LIST

Patent Literature

[0007] Patent Literature 1: JP Laid-Open Publication No. 2013-502445

Non Patent Literature

[0008] Non Patent Literature 1: Marti et al., Thromb. Haemost. 1999. Supplement 1: 44-52
[0009] Non Patent Literature 2: Matsumoto et al., VEGF Receptor Signal Transduction. Sci. STKE. 2001. re21
[0010] Non Patent Literature 3: US Ophthalimic Rev., 2013. 6:58-63

SUMMARY OF INVENTION

Technical Problem

[0011] The present invention has been achieved under such circumstances. A technical problem to be solved by the present invention is to provide a novel antibody that inhibits the physiological activity of VEGF by binding to a vascular endothelial growth factor (VEGF) with its high affinity for VEGF compared to the prior art to inhibit binding of VEGF to a VEGF receptor.

Solution to Problem

[0012] As a result of intensive studies to solve the problem, the present inventors have prepared an antibody that binds to VEGF with high affinity, have discovered that the antibody inhibits the physiological action of VEGF, and thus have completed the present invention.
[0013] That is, the present invention is as follows.
(1) A monoclonal antibody against VEGF that binds to a vascular endothelial growth factor (VEGF) with a dissociation constant of 1×10^{-11} mol/L or less.
(2) The monoclonal antibody according to (1) above, wherein the monoclonal antibody inhibits binding of a vascular endothelial growth factor (VEGF) to at least one receptor selected from the group consisting of vascular endothelial growth factor receptor-1 (VEGFR1) and vascular endothelial growth factor receptor-2 (VEGFR2).
(3) A monoclonal antibody that binds to a site to which the monoclonal antibody according to (1) or (2) above binds.
(4) The monoclonal antibody according to any one of (1) to (3) above, wherein the monoclonal antibody is a chimeric antibody or a humanized antibody.
(5) The antibody according to any one of (1) to (4) above, comprising CDR-H1 that comprises the amino acid sequence of SEQ ID NO: 14, CDR-H2 that comprises the amino acid sequence of SEQ ID NO: 16, and CDR-H3 that comprises the amino acid sequence of SEQ ID NO: 18.
(6) The antibody according to any one of (1) to (4) above, comprising CDR-L1 that comprises the amino acid sequence of SEQ ID NO: 20, CDR-L2 that comprises the amino acid sequence of Trp-Ala-Ser, and CDR-L3 that comprises the amino acid sequence of SEQ ID NO: 22.
(7) The antibody according to any one of (1) to (4) above, comprising:
CDR-H1 that comprises the amino acid sequence of SEQ ID NO: 14, CDR-H2 that comprises the amino acid sequence of SEQ ID NO: 16, and CDR-H3 that comprises the amino acid sequence of SEQ ID NO: 18; and